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PATENT
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Jacobus, *et al.*

Confirmation No.: 6080

Application No.: 10/716,283

Group Art Unit: 1624

Filing Date: November 18, 2003

Examiner: V. Balasubramanian

For: BIGUANIDE AND DIHYDROTRIAZINE DERIVATIVES

DATE OF DEPOSIT: November 20, 2006

I HEREBY CERTIFY THAT THIS PAPER IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE AS FIRST CLASS MAIL, POSTAGE PREPAID, ON THE DATE INDICATED ABOVE AND IS ADDRESSED TO THE COMMISSIONER FOR PATENTS, P.O. BOX 1450, ALEXANDRIA, VA 22313-1450.

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Sir:

PRE-APPEAL BRIEF REQUEST FOR REVIEW

Applicants respectfully request review of the final rejection in the above-identified application. No amendments are being filed with this request. This request is being filed with a Notice of Appeal. The review is requested for the reasons stated on the attached sheets. No more than five pages are provided.

REMARKS

Claims 1, 3 to 90, 99, and 100 are pending in this application. Claims 1, 3 to 90, and 99 are allowed. Claim 100 is rejected under 35 U.S.C. § 112, first paragraph, as allegedly not enabled because it is directed to preventing malaria. Reconsideration of Claim 100 in view of the remarks found hereinbelow is respectfully requested.

Claim 100 is directed to a method for protecting a patient susceptible to infection caused by exposure to *Plasmodium sp.* comprising the step of administering to said patient in need thereof an effective amount of one or more compounds according to claim 1. The method of claim 100 prevents a malarial infection from *Plasmodium sp.* by having a patient initiate drug therapy (chemoprophylaxis) prior to the time he risks exposure to *Plasmodia*, in the same manner as a number of other well-known and tested anti-malarial drugs are used to prevent malaria..

Background

Preventative treatment against malarial infections is well known. For many years, travelers have taken anti-malarial medications before they travel abroad to areas where there is significant risk of exposure to malaria. At the time the invention was filed, this preventative treatment method was recommended by the United States Government to protect travelers going to countries with malarial risk. Even today, taking anti-malarial drugs in this fashion is the recommended method of addressing the risk for malarial infections for those traveling to countries where there is significant risk of exposure. This recommendation and related discussion may be found, for example, at the U. S. Government's Center for Disease Control (hereinafter "CDC") website:

http://www.cdc.gov/malaria/travel/index.htm#protectyourself

A map found on the CDC website indicates those areas where both malaria is transmitted and travelers are at risk of contracting the disease. The same web page, under the heading, "**Preventive Measures Taken By Travelers**", states that "[I]individual measures, such as taking an effective anti-malarial drug and preventing mosquito bites, are the most important factors in minimizing risk (emphasis added). While other risk factors may be difficult to

change or avoid, travelers can greatly reduce their risk of malaria by following recommended travel **precautions** (emphasis added)."

A major use of commercially available anti-malarial pharmaceutical drugs, including Daraprim®, Malarone™, Plaquenil®, Lariam®, and Aralen®, was and remains their administration in this type of preventive therapy (chemoprophylaxis). Such analogous preventative preventive therapy using compounds of the present invention is the subject matter of claim 100 for which this Pre-Appeal Review of the final rejection under 35 U.S.C. § 112, first paragraph, is requested.

The particular question to be addressed here is whether one ordinarily skilled in the relevant art, once equipped with the teachings of the present invention and the relevant art, could use the method to which Claim 100 is directed. That is, based on the specification and information available to him[1] at the time the application was filed,[2] could one of ordinary skill reasonably have expected that a compound of the present invention, shown to be effective against a classic form of malaria (*Plasmodia*) in a standard laboratory test, would be effective in preventing malarial infection by administering the compound to the patient prior to exposure to the infection.

Information Available to the Skilled Artisan at the Time the Invention was Filed.

One of ordinary skill in malarial prevention and/or treatment understood prevention (prophylaxis) in a malarial context to mean chemoprophylaxis.[3] The skilled artisan also

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[1] "*Malaria Prophylaxis Guidelines for the Prevention of Malaria in South Africa*" ,a report issued by the South Africa Department of Health on March 1, 2003 in close collaboration with malarial experts. Applicants further bring to the attention of the Examiner that the South African report indicated the guidelines were in keeping with the existing World Health Organization's guidelines for the prevention of malaria. A copy of the South African report was provided for convenience during prosecution. The report may also be found on the Internet at http://www.doh.gov.za/docs/factsheets/guidelines/malaria/prevention.pdf

[2] November 18, 2003.

[3] "Chemoprophylaxis may refer to absolute prevention of infection (i.e. causal prophylaxis) or to suppression of parasitaemia and its symptoms (i.e. suppressive or clinical prophylaxis). Drugs, which act on the erythrocytic stages of the parasite (i.e. once the parasite has invaded the red blood cells) are known as blood schizonticides and are suppressive prophylactics. These medicines suppress the disease by destroying the asexual parasites but have no effect on the intrahepatic forms. Examples of blood schizonticides include chloroquine, mefloquine, quinine, halofantrine, pyrimethamine, sulphonamides and sulfones. If prophylaxis is continued until there are no more parasites entering the blood, then a suppressive cure is achieved" (from "*Malaria Prophylaxis Guidelines for the Prevention of Malaria in South Africa*" ,a report issued by the South Africa Department of Health on March 1, 2003).

knew that the most widely used anti-malarial compounds at the time the invention was filed, including Daraprim®, Malarone™, Plaquenil®, Lariam®, and Aralen®, were recognized as active against *Plasmodia* infections. Further, he recognized that these same compounds were indicated for use in preventive therapy (*i.e.,* as chemoprophylactic agents in either absolute or suppressive prophylaxis). Support for this prophylactic use of anti-malarials may be found in the "*Physician's Desk Reference*", 56th Ed, **2002**.[4] This reference not only provides the indication of preventive use for these anti-malarial agents, but discloses dosage levels, contraindications, pharmacology, adverse reactions, and the like. Therefore, one of ordinary skill in the art would understand that, in general, drugs which are used to treat acute malarial infections arising from *Plasmodia* may also be used in prophylactic treatment as a preventative measure against this same infection. Similarly, based on the guidance provided in the "*Physician's Desk Reference*", 56th Ed, **2002**, the skilled artisan would understand how best and how much of the present compounds to administer to effectively provide the desired protection from *Plasmodia*.

The Enablement of the Present Invention

The compounds of the present invention have biological activity against *Plasmodia*. In the standard Mouse Malarial Model (Thomson Model) used by those of ordinary skill in the art to ascertain anti-malarial activity[5], the compounds of the present invention, like commercially available anti-malarial drugs such as Daraprim®, Malarone™, Plaquenil®, Lariam®, and Aralen®, have been shown to have biological activity against *Plasmodia*. Earlier in this prosecution, the Patent Office acknowledged the present compounds' biological activity against *Plasmodia* which is further evidenced by the Patent Office's allowance of Claim 99, directed in part to treatment of a person infected already infected with *Plasmodium sp* with compounds of the present invention.

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[4] A best available copy of the appropriate pages was also submitted to the USPTO for convenience on October 25, 2006. Comments regarding prophylactic use are found under the Indications Section for each of the anti-malarial drugs Daraprim®, Malarone™, Plaquenil®, Lariam®, and Aralen®.

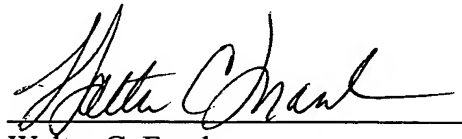
[5] The Thompson model, also known as the six-day model, is described in "*Handbook of Experimental Pharmacology*", vol. 68/I, 1984, Springer Verlag, W Peters and W. H. G. Richards, editors beginning at page 231. The 1969 full reference to the Thompson (or six-day) model is cited in "*Handbook of Experimental Pharmacology*" at page 263. A copy of the Appropriate pages from the in "*Handbook of Experimental Pharmacology*" were provided to the USPTO for convenience at the time the after final response to Office Action was filed (October 25, 2006).

CONCLUSION

As hereinabove described, the present compounds' activity against *Plasmodia* and the compounds' use to treat already infected hosts has been established through standardized testing procedures. The compounds of the present invention have this activity in common with other commercial drugs. Those same commercial drugs used to treat already-*Plasmodia*-infected hosts were also indicated for chemoprophylaxis against possible infections due to *Plasmodia* in the then available "*Physician's Desk Reference*", 56th Ed, **2002**. That same reference provides the recommended manner in which such drugs should be given and necessary precautions to be taken in their administration. Therefore, absent evidence to the contrary, one of ordinary skill in the art, armed with the knowledge of the present compounds' activity against *Plasmodia* in a standard test and other publicly accessible information, would reasonably understand not only that the compounds of the invention could be used but also how they might be administered ***to prevent*** malarial infections arising from *Plasmodia* (through chemoprophylaxis).

For these reasons, Applicants submit that claim 100 is adequately enabled, and respectfully request that the rejection to Claim 100 under 35 U.S.C. § 112, first paragraph be withdrawn.

Date: ***November 20, 2006***



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